CHEMOPROPHYLAXIS OF POLIOMYELITIS*

(A PROGRESS REPORT)†

By E. W. SCHULTZ, M.D.
AND
L. P. GEBHARDT, M.A.
Stanford University

THAT the olfactory nerve is the common portal of entrance of poliomyelitis virus is now well established: Schultz and Gebhardt, 1934;[1] Brodie and Elvidge, 1934;[2] Lennette and Hudson, 1935.[3] It is also clear from recent experimental studies that the administration of specific immune serum does not afford significant protection against subsequent intranasal instillation of monkeys with poliomyelitis virus: Schultz and Gebhardt, 1935.[4] The failure of immune serum to afford protection against instranasally-inoculated virus may be explained by the fact that the terminals of the olfactory nerve are so situated that they cannot be effectively guarded by immune plasma, and further explained by the fact that virus once established in the olfactory or other nerve tracts is, for the most part, safely out of reach of humoral antibodies. It has, moreover, been quite conclusively shown that the injection of poliomyelitis vaccines, at best, results in the production of humoral antibodies, with no recognizable increase in tissue resistance, or significant protection against virus administered by the intranasal route: Schultz and Gebhardt, 1935;[5] Olitzky and Cox, 1936;[6] and Hudson, Lennette and Gordon, 1936.[7] These observations seem to leave little prospect of a practical solution of the poliomyelitis problem by orthodox means. It has become necessary, therefore, to seek a solution in new directions.

RECENT STUDIES REPORTED IN THE LITERATURE

In 1934, Olitzky and Cox[8] made the interesting observation that a dilute tannic acid solution in distilled water, dropped into the nostrils of white mice three times a day on three successive days, served to protect these animals against intranasal instillation of equine encephalomyelitis virus administered on the fourth day. The protection afforded was transient, since it disappeared almost completely by the tenth day. Soon after, Armstrong (1935)[9] made similar observations on experimental St. Louis encephalitis in mice, using sodium alum as the protecting agent.

AUTHORS' STUDIES

Without being aware of these latter interesting observations, we undertook, in the spring of 1935, to test the possibility of protecting monkeys against intranasal infection with poliomyelitis virus by chemical means. We first tried tannic acid; but finding the results of two experiments somewhat irregular, we turned our attention to picric acid and certain other agents. Soon after (May 31, 1935), Armstrong and Harrison[10] reported that monkeys which had previously received intranasal treatment with 4 per cent sodium aluminum sulphate, exhibited a high incidence of protection against subsequent intranasal instillation of virus. The duration of the protection was not determined. Several months later, in January, 1936,[11] these observations were confirmed by Sabin, Olitzky and Cox, who found that 4 per cent tannic acid also afforded temporary protection. On February 5, 1936, we[12] reported to the Pacific Coast Section of the Society of Experimental Biology and Medicine observations which indicate that protection is also afforded by picric acid, p.-nitrophenol, trinitrocresol and by mercurochrome. These observations showed that the protection afforded may, in some instances, be of several months' duration. Late in the same month (on February 28) a paper by Armstrong and Harrison[13] appeared, dealing with further studies on chemical protection of mice against intrasanally-instilled St. Louis encephalitis virus, and with the protection afforded monkeys by picric acid against intranasally-instilled poliomyelitis virus. Although they made no observations on the actual duration of the protection afforded, and their technical procedures were not altogether like ours,‡ the results were essentially the same.

SUMMARY ON THE AUTHORS' OBSERVATIONS

We wish at this time to present a summary of our observations to date, and to indicate the possibilities offered by further investigations in this field.

Of sixteen monkeys given three successive daily intranasal irrigations with 1 per cent aqueous solution of picric acid, only three animals succumbed to intranasal instillations of 10 per cent virus suspensions (three instillations on one day) administered one to eight days following the treatment; one of those developing poliomyelitis had been given intranasal washes with saturated aqueous lithium carbonate, in an effort to remove the picric acid from the nasal mucosa. Of the thirteen monkeys which survived, ten escaped a second instillation of virus administered eighteen to thirty-nine days after treatment; the three which became infected received the virus instillations twenty-seven, thirty-one and thirty-nine days after treatment with picric acid. Only eight of the survivors have been tested further. Of these, five escaped a third instillation of virus administered forty to sixty-eight days after the treatment. Of the remaining five animals, two out of three which had gone sixty days, developed poliomyelitis after a fourth instillation of virus. One resisted nasal virus seventy-three, ninety-four, 108 and 129 days and one eighty-nine days after the original treatment. One of the latter two died of an intercurrent infection 110 days after the original picric acid treatment; the remaining animal withstood a

* From the Department of Bacteriology and Experimental Pathology, Stanford University, California.

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‡ The monkeys are deeply anesthetized, placed in a vertical position, and the nasopharynx thoroughly irrigated with about 30 cubic centimeters of the chemical.

fifth intranasal instillation of virus ninety-two days after treatment, but developed poliomyelitis after a sixth virus instillation 121 days after the treatment with picric acid.

Of six monkeys treated with three nasal washes of 1 per cent picric acid neutralized to pH 6.9, three failed to resist inoculation ten days after the third treatment. Two of the remaining three monkeys have further resisted inoculation thirty-one and fifty-five days after treatment, while one died of tuberculosis seven days after the second virus inoculation. Each picric acid wash was preceded by a nasal spray of 0.25 per cent neosynephrin.

In still another experiment twenty monkeys were given intranasal sprays with 1 per cent picric acid in physiological saline solution on three successive days and thereafter once a week. Virus instillations were begun one day after the third treatment and continued daily, with the exception of the days on which the picric acid treatments were administered. This has to date been carried on for a period of about three weeks, with the result that nine of the ten controls used have developed poliomyelitis, while only six of the twenty animals treated have come down with the disease. The daily virus instillations and weekly treatments with picric acid are being continued with new sets of controls.

ON THE RELATIVE EFFICACY OF REPEATED WASHINGS

Observations on the relative efficacy of repeated washings with lower concentrations of picric acid are too limited and irregular to justify detailing here.

Of a total of thirteen monkeys given three successive daily nasal irrigations with 2 per cent aqueous solution of mercurochrome (No. 220 solution), one only developed poliomyelitis following intranasal instillation of virus administered two to six days later; one died of an intercurrent infection twenty-five days later; of the eleven remaining animals all have resisted intranasal instillation of virus twenty-three to thirty-one days after the treatment (one died of an enteritis twelve days, and one of tuberculosis two days following the second virus inoculation). The remaining nine animals were given a third instillation of virus on the thirty-eighth to fifty-second day after treatment (one died later of tuberculosis and one of enteritis). One only developed poliomyelitis. The remaining six monkeys were inoculated again fifty-eight to seventy-nine days after treatment. This time two developed poliomyelitis (one given virus fifty-eight and one seventy-three days after treatment). One died of enteritis two days after inoculation. (It might be well to note that the majoriy of the animals are observed from twenty-one to thirty days before each reinoculation with virus).

Of twelve monkeys which had been given intranasal irrigations with 1 per cent mercurochrome on three successive days, ten resisted intranasal instillation of virus one to eighteen days later. These two developed the disease when inoculated eleven days after treatment. One died twenty-two days later of an intercurrent disease. The remaining nine monkeys were reinoculated thirty-one to sixty days after treatment. One inoculated thirty-two days and one fifty-three days after treatment developed the disease, while one died of an enteritis two days after the third virus inoculation. Of three animals which had been given the mercurochrome (1 per cent) by simply dropping 2 cubic centimeters of the dye into the nostrils once a day on three successive days, only one developed poliomyelitis when tested eleven days after the third dye wash. The remaining two monkeys have resisted nasal virus thirty-two, fifty-three and seventy-seven days, respectively, after the original treatments.

Seven out of seven treated monkeys resisted virus when tested ten days after they were treated on three successive days with 1 per cent mercurochrome (phosphate-saline pH 8.6). These seven monkeys were reinoculated thirty-one days after treatment, and this time two animals developed the disease. These monkeys received a nasal spray of 0.25 per cent neosynephrin one-half hour before each mercurochrome wash.

Five monkeys received a similar treatment (but without neosynephrin) with 0.5 per cent mercurochrome and virus given nasally eleven days after the third dye treatment; three developed the disease; one died of an enteritis on the tenth day, and one survived the virus inoculation. This surviving monkey has further resisted nasal virus thirty-two and fifty-three days after the original mercurochrome treatment. Of six monkeys receiving three successive daily nasal washes with 0.5 per cent mercurochrome (phosphate-saline pH 8.6) and sprayed nasally with 0.25 per cent neosynephrin one-half hour before each dye treatment, only one developed the disease when inoculated ten days after the above treatment. One of these animals died of an enteritis three days after the virus inoculation. The remaining four animals were reinoculated thirty-one days after treatment, and this time two developed the disease. Three other monkeys were given three successive daily nasal washes with 0.25 per cent mercurochrome, and then given virus nasally two days after the third dye treatment; all three developed the disease.

EFFECTS OF OTHER CHEMICAL AGENTS

The effects of a number of other chemical agents have been less extensively studied. Four monkeys given intranasal washes with 1 per cent aqueous paranitrophenol resisted instillations of virus two to seven days after treatment. Three resisted a second instillation of virus thirty-one to thirty-nine days after treatment, while one developed poliomyelitis when inoculated thirty-one days after treatment, and one died with an enteritis eighteen days later. The two remaining animals resisted a third instillation of virus administered fifty-two days after the treatment. One, however, succumbed to poliomyelitis following a fourth instillation seventy-three days after chemical treatment and one died of tuberculosis twenty-nine days after the fourth instillation of virus.

Of three monkeys treated with a 0.5 per cent aqueous solution of paranitrophenol one resisted an instillation of virus two days later; one developed typical poliomyelitis, while one died of an enteric disturbance nine days after inoculation. When a further test was carried out twenty-three days after the treatment, the one monkey remaining developed typical poliomyelitis.

More or less long protection also seems to be afforded by 1 per cent trinitrocresol; by 1 per cent silver nitrate (two monkeys protected two, twenty-three and forty-four days); by 5 per cent protoargentum; by 10 per cent argyrol; by 2 per cent erythrosine; by 1 per cent neutral acriflavine; by 1 per cent zinc sulfate (three monkeys protected two, twenty-three, forty-four and sixty-eight days).

Three monkeys were protected by 1 per cent thionin for at least twenty-three days; two of these died of an enteritis, one twenty-one days and one twenty-two days after the second virus inoculation. The remaining monkey has resisted virus inoculation forty-four, fifty-eight and seventy-nine days after the original thionin treatment.

Three monkeys treated with 0.5 per cent thionin resisted virus instillation two days later. One died of an enteritis twenty-nine days after the virus inoculation. The two remaining monkeys have resisted inoculation twenty-three, forty-four and sixty-eight days after treatment.

Little or no protection was afforded by 1 per cent ammonium picrate, 1 per cent congo red, 1 per cent trypan blue, 1 per cent sodium fluorescence (uranin), 1 per cent trypan red, 1 per cent eosin yellowish, 0.25 per cent mercurochrome or 10 per cent normal monkey cord.

IN CONCLUSION

It is apparent that the protected animals eventually will develop the disease in the absence of continued chemical treatment, provided the virus inoculations are continued for a sufficiently long period of time.

A total of 112 controls served in carrying out these studies, 84.8 per cent of which have developed poliomyelitis.

While various chemical compounds are more or less effective in protecting monkeys against intranasal inoculation with poliomyelitis virus, it does not follow, of course, that all of these are equally applicable to man. Of those we have studied thus far, 1 per cent picric acid in physiological saline seems in general the most suitable; not only because its effectiveness has been quite definitely established, but also because it is, in itself, essentially harmless and comparatively nonirritating. We would suggest that the solution be applied with an atomizer on three successive or alternate days, and thereafter once every week or ten days during the period of an epidemic. Since the solution should be thoroughly applied to the olfactory area, it is desirable to have the treatments carried out under the supervision of a competent nose and throat specialist, who would consider the anatomic conditions which might ordinarily interfere with making the necessary contact with this area.

Stanford University.

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HEAT PRODUCING APPLIANCES: THEIR COMPARATIVE VALUE IN THE TREATMENT OF PROSTATIC INFECTIONS*

By JAMES B. HERRING, M. D.
San Francisco

DISCUSSION *by Norman N. Epstein, M.D., San Francisco; Robert V. Day, M.D., Los Angeles.*

RAISING the temperature of the prostate has therapeutic value. I believe most, if not all of us, will subscribe to that statement. It leaves only the question as to what is the best method of producing the heat.

METHODS OF TREATMENT

The fact that there are so many types of treatment is evidence that a satisfactory method has not been evolved. Massage, irrigation, dilatation and posterior urethral instillations have been used, but with varied and not entirely satisfactory results. Vaccines, injections of various types, and numerous appliances have been employed. The keystone has been digital massage, a thoroughly unscientific procedure, but so far, the best. Acceptable conclusions, however, have never been reached, because they have been based on "cure," and the time consumed in producing cure, when we have no entirely agreeable method of determining when cure has been produced.

METHODS OF DETERMINING CURE

By signs.—Examining prostate rectally, most of us feel, is unreliable. Tenderness and, especially,

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